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Fear-Potentiated Startle Conditioning to Explicit and Contextual Cues in Gulf War Veterans With Posttraumatic Stress Disorder

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Aversive conditioning to explicit and contextual cues was examined in Gulf War veterans with and without posttraumatic stress disorder (PTSD) by use of the startle reflex methodology. Veterans participated in a differential aversive conditioning experiment consisting of 2 sessions separated by 4 or 5 days. Each session comprised two startle habituation periods, a preconditioning phase, a conditioning phase, and a postconditioning extinction test. In contrast to the non-PTSD group, the PTSD group showed a lack of differential startle response in the presence of a conditioned stimulus with or without an unconditioned stimulus in Session 1 and an increase in the baseline startle response during Session 2. The PTSD group also exhibited normal differential conditioning following reconditioning in Session 2. These data suggest that individuals with PTSD tend to generalize fear across stimuli and are sensitized by stress.

Exaggerated startle has been and continues to be a clinical feature of posttraumatic stress disorder (PTSD; American Psychiatric Association, 1994; Kardiner, 1941). Nevertheless, it is still unclear whether or not startle is abnormally elevated in individuals with this condition. Increased responses (Butler et al., 1990; Morgan, Grillon, Southwick, & Charney, 1996; Orr, Lasko, Shalev, & Pitman, 1995), normal responses (Grillon, Morgan, Southwick, Davis, & Charney, 1996; Orr, Solomon, Peri, Pitman, & Shalev, 1997), and even reduced responses (Ornitz & Pynoos, 1989) have been reported. A better understanding of this issue is relevant because a great deal is known about the neurobiological substrates of stress-induced alterations of startle in animals (Davis, 1992). Therefore, an analysis of the causes of exaggerated startle in PTSD could provide important insights into central nervous system abnormalities in this disorder. We found exaggerated startle in Vietnam veterans with PTSD throughout experiments in which stressful procedures were used (Morgan, Grillon, Southwick, Davis, & Charney, 1995; Morgan, Grillon, Southwick, Nagy, et al., 1995) but not in the absence of experimental stress (Grillon et al., 1996). On the basis of these findings, we hypothesized that combat veterans with PTSD suffer from an enhanced sensitivity to stressful experimental contexts.

This hypothesis was tested in another study with Vietnam veterans with PTSD (Grillon, Morgan, Davis, & Southwick, 1998) that investigated startle in two sessions: (a) in the absence of experimental stress and (b) a few days later during an experiment in which aversive shocks were anticipated. In the latter, "verbal threat" experiment, participants were told that they could receive unpleasant shocks during threat periods but not during safe periods signaled by lights of different colors. Baseline startle in the patients with PTSD did not differ from that in the age-matched combat and civilian comparison groups during the 1st day of testing in the absence of stress. During the 2nd day, however, startle was elevated throughout the testing procedure, even before the shock electrodes were attached to the participants, suggesting that fear had been generalized to the experimental context. Of note, both the patient and the comparison groups showed equivalent potentiated startle to the threat signal (fear-potentiated startle). This finding (normal fear-potentiated startle to threat signals but elevated baseline startle during the entire testing procedure on Day 2) suggests that the veterans with PTSD had differential aversive responses to explicit (e.g., the threat signal) and contextual (e.g., the experimental room) stimuli. These results are particularly meaningful given recent animal data suggesting that different brain structures are involved in these two types of fear (Davis, Gewirtz, McNish, & Kim, 1995; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; see below).

The aim of the present study was to extend our investigation of responses to aversive explicit and contextual cues in combat veterans with PTSD by using a conditioning procedure. Conditioning procedures present several advantages over verbal threat procedures. They are more closely related to animal studies, and they enable learning processes to be examined. Two learning processes are especially relevant to the present study: context conditioning and differential conditioning. Context conditioning refers to the learned fear that develops to the experimental context during an aversive conditioning procedure. For example, during aversive conditioning, animals are placed in an experimental chamber in which they are exposed to a brief neutral stimulus (e.g., a light)

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that is repeatedly paired with an aversive unconditioned stimulus (US; e.g., a shock). Subsequently, presentations of the neutral stimulus produce a constellation of physiological and behavioral responses that are used to index a central state of fear. The neutral stimulus is referred to as a *discrete* or *explicit* conditioned stimulus (CS) because it is presented for a short period and its physical characteristics are specifically defined. In addition to showing fear to the explicit CS, studies suggest that animals rapidly learn to fear the context in which the shocks are administered (i.e., the cage) (Blanchard & Blanchard, 1972; Bolles & Fanselow, 1980). The environmental context consists of the various static contextual cues that are available to the animal at the time of the initial conditioning. Collectively, these cues are referred to as the *contextual* CS. On the basis of our previous findings, veterans with PTSD would be expected to show increased contextual fear conditioning.

During differential conditioning experiments, participants are presented with two CSs (CS+ and CS−), only one (CS+) being reinforced by a US. Participants gradually learn to fear the CS+ but not the CS−. If, as we have hypothesized (Grillon et al., 1998), individuals with PTSD tend to generalize fear, they would be expected to exhibit fear to both the CS+ and the CS− and, consequently, to show reduced (or absent) differential conditioned responses to the CS+ and the CS−.

The startle reflex, a cross-species response to intense stimuli with abrupt onset, is an experimental model that bridges the gap between human research and animal research on stress and anxiety (Davis, 1992). There is substantial evidence indicating that startle is sensitive to aversive learning. Startle is potentiated when elicited in the presence of a CS previously associated with an aversive outcome (e.g., a shock). This phenomenon is referred to as fear-potentiated startle to an explicit cue. However, a more general elevation of startle is found when the animals are placed back in the aversive training context (Campeau et al., 1991; Davis et al., 1995). Lesion studies suggest that although the amygdala is associated with fear-potentiated startle to an explicit cue (Hitchcock & Davis, 1986), the bed nucleus of the stria terminalis (BNST) may be more responsible for the general enhancement of startle by contextual cues (Davis et al., 1995). Furthermore, through techniques other than the startle reflex technique, it has been shown that the hippocampus is also involved in contextual fear conditioning (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). These findings suggest that different structures mediate explicit cue conditioning and contextual fear conditioning.

We have successfully established contextual fear conditioning in humans by using the startle reflex methodology (Grillon & Davis, 1997). Two groups of healthy participants took part in a single-cue aversive conditioning experiment during which the same conditioning procedure was given on 2 separate days separated by 4 or 5 days. The aversive US and the CS were paired in one group (paired group), whereas they were unpaired (i.e., the US was administered randomly in the absence of a CS) in the other group (unpaired group). A third group (reference group) underwent nonaversive conditioning. This group served as a control for evaluating the long-term habituation of startle. When the three groups were tested on the 2nd day, only the reference group showed a reduction in or long-term habituation of startle. There was evidence of contextual fear conditioning in the unpaired group because startle was enhanced from Day 1 to Day 2. The paired group also showed contextual fear conditioning, although to a lesser extent than the unpaired group. In this group, startle on Day 2 was intermediate between that in the reference group and that in the unpaired group.

We designed the present experiment to examine contextual fear conditioning in Gulf War veterans with PTSD by use of a similar procedure. Participants took part in an aversive conditioning experiment over two sessions on separate days. We expected veterans with PTSD to show increased context conditioning compared to veterans without PTSD. We chose a procedure in which the shock US was paired with the CS+ during conditioning. Although this procedure does not result in as much contextual fear conditioning as unpaired presentation of the CS and the US, it allows for the examination of the acquisition, retention, and extinction of fear conditioning to the explicit cue (i.e., the CS+). In addition, we used a differential conditioning procedure to examine stimulus generalization to CS−. As indicated above, if individuals with PTSD tend to generalize fear across stimuli, such a response should be associated with deficits in differential conditioning and/or a lack of extinction.

Method

Participants

Individuals participating in this study consisted of 13 nonmedicated male Gulf War veterans with PTSD and 14 male Gulf War veterans without PTSD. All the participants were from the same unit in the Gulf War. While deployed in the desert, they were subjected to SCUD missile attacks, witnessed the loss of the lives of three unit members, and were exposed to the gross disfigurement of bodies (burned, dismembered, and decapitated enemy soldiers).

All participants gave written informed consent. Two participants in the non-PTSD group had virtually no eye-blink reflex and were excluded from the analysis. One patient with PTSD participated in the 1st session but did not return for the 2nd one.[1] The final sample consisted of 12 veterans with PTSD and 12 veterans without PTSD. We recruited patients from our outpatient PTSD clinic. Each patient with PTSD met full criteria for PTSD, according to the *Structured Clinical Interview for DSM–III–R* (Spitzer, Williams, Gibbon, & First, 1990a). One veteran with PTSD had a comorbid history of alcohol dependence. The other veterans with PTSD did not meet criteria for any other comorbid psychiatric disorders. None of the veterans without PTSD endorsed more than 3 of the 17 items on the PTSD Symptom Checklist (Foa, Riggs, Dancu, & Rothbaum, 1993), and none of these endorsements were rated in terms of severity as greater than 2 on a scale of 1 to 5 (1 = none; 2 = mild; 3 = moderate; 4 = severe; and 5 = extreme). None of the veterans without PTSD met the criteria in the *Structured Clinical Interview for DSM–III–R* for any psychiatric or substance abuse disorders (Spitzer, Williams, Gibbon, & First, 1990b).

Participants were free of illicit substance use, as determined by urinary toxicology screens, and had normal binaural hearing for 500-, 1000-, and 2000-Hz tones at 20 dB (sound pressure level). Mean ages did not differ significantly between the two groups, $t(22) = 1.2$ (Table 1). Each veteran

[1] The veteran with PTSD who did not return for the second session was extremely anxious in the first session. His trait anxiety, state, anxiety, and Mississippi scores were 61, 39, and 144, respectively. He had a marked exaggerated baseline startle. For comparison with the other veterans (see Figure 1), the magnitudes of his startle response were 1,373, 1,279, and 477 μV in Habituation 1, in Habituation 2, and during the ITI of the preconditioning phase, respectively. After conditioning, his startle response was increased by 431 μV during the CS− and by 1,038 μV during the CS+.

Table 1
Ages and Mississippi, State Anxiety, and Trait Anxiety Scores in Combat Veterans With and Without Posttraumatic Stress Disorder (PTSD)

Parameter	PTSD group		Non-PTSD group	
	M	*SD*	*M*	*SD*
Age	33.6	6.2	38.4	11.7
Mississippi	120.3	17.0	63.0	8.9*
Trait anxiety	48.5	13.5	32.0	7.4*
State anxiety, Session 1	46.0	8.3	30.2	7.4*
State anxiety, Session 2	43.8	7.2	29.0	7.7*

*$p < .001$.

completed the Mississippi Scale for Combat-Related PTSD to assess the intensity of the PTSD symptoms (Keane, Caddell, & Taylor, 1988). Mean Mississippi scores were significantly higher in the PTSD group than in the non-PTSD group, $t(22) = 10.3$, $p < .0009$ (see Table 1). Participants rated their state and trait anxiety with the State-Trait Anxiety Inventory (Spielberger, 1983) on arrival in the laboratory in Session 1. They also rated their state anxiety on arrival in the laboratory in Session 2.

Apparatus and Physiological Recording

The CS+ and CS− were two colored lights (blue and green 60-W bulbs counterbalanced between groups and across participants) located on a table about 1 m in front of the participants. The US was an electric shock (2.0 mA, 5-ms duration) produced by a Constant Current Unit (Grass Instruments) and administered through two pure-tin disk electrodes placed on the inside of the left wrist. The acoustic startle probes were 40-ms 102-dB bursts of white noise with a nearly instantaneous onset generated by a noise generator (S81-02; Coulbourn Instruments), gated through an Audio Mixer Amplifier (S82-24; Coulbourn Instruments), and delivered binaurally through headphones. The eye-blink reflex was measured by recording activity from the orbicularis oculi muscle below the left eye with two disk electrodes (Ag-AgCl; 5-mm inside diameter). The ground electrode was placed on the left arm. The impedance level was kept below 5 Ω. Electromyographic (EMG) activity was amplified (20,000 times) and filtered (90 to 1000 Hz) with a Bioamplifier (S75-01; Coulbourn Instruments), full-wave rectified with a Contour Following Integrator (S76-01; Coulbourn Instruments) with a time constant set at 10 ms, and continuously digitized at 1 kHz.

Procedure

During testing, participants sat in a reclining chair. The experiment consisted of a differential conditioning procedure that was performed over two testing sessions (Session 1 and Session 2) separated by 4 or 5 days. The two sessions were identical, except for the number of CSs presented during the postconditioning phase (see below). There were five separate phases in each session: (a) Startle Habituation 1, (b) Startle Habituation 2, (c) preconditioning, (d) conditioning, and (e) postconditioning. During Startle Habituation 1, five blocks of two startle probes were delivered. The shock electrodes were not attached during this period. The purpose of the two habituation phases was to reduce initial startle reactivity and to assess the effect of placing the shock electrodes. Our previous study of contextual fear conditioning suggested that contextual fear was greater after the shock electrodes were placed (Grillon & Davis, 1997).

Approximately 6 min after Startle Habituation 1, the shock electrodes were placed on the participants' wrists and Startle Habituation 2 was started. It consisted of three blocks of two startle probes. Startle Habituation 2 was immediately followed by the preconditioning phase to assess the unconditioned effects of the CS+ and CS− on startle (the US was not administered). The preconditioning phase consisted of two blocks of two CS+'s and two CS−'s (total of four CS+'s and four CS−'s). The conditioning phase consisted of two blocks of five CS+'s and five CS−'s. In each block, four of the five CS+'s terminated with the administration of a shock (US). The postconditioning phase examined the amount of conditioning (the US was not administered). During the postconditioning phase, there were three blocks of two CS+'s and two CS−'s in Session 1 and five blocks of two CS+'s and two CS−'s in Session 2.

The duration of each CS was 4.5 s. In the pre- and postconditioning phases, startle probes were presented 4 s following the onset of each CS. Two startle probes were also presented between CSs (i.e., during the intertrial interval [ITI]) in each block. During the conditioning phase, five startle probes were delivered in each block, one during the CS+ that was not associated with a shock, one during one of the five CS−'s, and three between CSs.[2] The CS ITI varied from 30 to 50 s. Within each block, CS+, CS−, and startle probes during the ITI alone were presented in a quasi-random order. During the conditioning phase, no more than two CSs of the same type (e.g., CS+) were presented consecutively.

The participants were told (1) that the blue and green lights (i.e., the CSs) would be turned on and off several times, (2) that unpleasant shocks would occasionally be administered, and (3) that they would hear relatively loud sounds during the procedure that they should ignore. No instruction regarding the CS–US contingency was given. These instructions were repeated in Session 2.

At the end of each session, participants' knowledge of the CS–US relationship was investigated by asking them to indicate whether the shocks were associated with the CS+ or the CS− or were administered in a nonsystematic manner. Participants could also indicate that they did not know the answer to this question.

Data Reduction and Data Analysis

Peak eye-blink reflex amplitude was determined as the largest deflection of the integrated EMG signal between 21 and 100 ms following stimulus onset. Peak amplitude was expressed relative to the mean EMG activity during the 50-ms period prior to stimulus onset. A zero-response score was assigned if no response was detectable. Zero-response scores were included in the data analysis (magnitude scores). Trials were rejected if the baseline EMG activity was unstable or peak eye blink occurred within 20 ms following probe onset. The percentages of discarded trials were similar in the PTSD and non-PTSD groups (1.2 and 1.3%, respectively).

The raw data were analyzed by mixed-factor analyses of variance (ANOVA) with repeated measures. Results were also analyzed with *z* scores. In general, very similar results were obtained with these two analyses. Results based on raw scores are reported. However, in two instances different results were obtained with raw scores and *z* scores. For these, results based on both raw scores and *z* scores are reported. Reduced

[2] When the study was designed, there was little information on aversive conditioning studied by the startle methodology. In Hamm et al.'s (1993) study, no startle probes were delivered during acquisition. We initially thought that delivering startle probes during the CS in the conditioning phase might interfere with acquisition. We were also concerned with the possibility that if no startle stimuli were presented during the conditioning phase, participants might associate the lack of startle stimulation with the presence of US and vice versa. We decided to take an intermediate approach and to deliver startle stimuli during a few but not all CSs in the conditioning phase. As a result, the acquisition process cannot be assessed satisfactorily. We now know that presenting startle probes during conditioning phases does not seem to interfere with acquisition (e.g., Hamm & Vaitl, 1996).

degrees of freedom (Geisser–Greenhouse) were used when appropriate to counter violations of the sphericity assumption underlying ANOVA with repeated measures.

The main hypotheses of the study were that veterans with PTSD would exhibit greater contextual fear and less differential conditioning than veterans without PTSD. The data analysis of contextual fear conditioning was based on the methods of a recent study of contextual fear conditioning in healthy participants (Grillon & Davis, 1997). Contextual fear was examined by comparing the magnitudes of startle in Session 1 and Session 2. Startles to probes delivered during Habituation 1 and Habituation 2 and during the ITI of the preconditioning phase were included in this analysis. Preliminary analyses indicated that there was no group difference in the rate of startle habituation within each of these phases. Consequently, the data were averaged across blocks within each phase. These data were entered into a Group (non-PTSD, PTSD) × Phase (Habituation 1, Habituation 2, preconditioning) × Session (1, 2) ANOVA. The magnitude of startle was expected to increase in the PTSD group and to decrease or to remain unchanged in the non-PTSD group from Session 1 to Session 2. Thus, significant Group × Session interactions were expected.

Differential conditioning data were analyzed with planned comparisons. For each phase, startle magnitudes were averaged within block for each trial type (ITI, CS+, and CS−). Differential conditioning was assessed by comparing the magnitudes of startle during CS+ and CS− in Group (non-PTSD or PTSD) × Trial Type (CS+ or CS−) × Block (n) ANOVA in the conditioning and postconditioning phases of each session (n = 3 for each phase, except for the postconditioning phase of Session 2, where n = 5). Unlike the veterans without PTSD, the veterans with PTSD were expected to show no or little differential conditioning. Significant Group × Trial Type interactions were expected. To examine the generalization of conditioned fear to the CS−, startles during ITI and CS− were compared with similar ANOVA: Group (2) × Trial Type (ITI, CS−) × Block (n). Startle was expected to be potentiated by the CS− in the PTSD group but not in the non-PTSD group, resulting in significant Group × Trial Type interactions.

In addition to these tests of the main hypotheses, retention of differential conditioning was examined with Session 2 preconditioning data in a Group (2) × Trial Type (CS+, CS−) × Block (2) ANOVA. The veterans with PTSD were expected to show little or no differential conditioning and to show potentiation of startle to both CSs. On the basis of a review by Mineka and Tomarken (1989) suggesting that the retention of fear inhibition is weaker than the retention of fear excitation and that fear tends to be generalized with the passage of time, some loss of differential conditioning was expected in the veterans without PTSD. Hence, no predictions were made for group differences in the retention data.

Results

Contextual Fear Conditioning

The results obtained during Habituation 1 (shock electrodes not attached), Habituation 2 (shock electrodes attached), and the ITI of the preconditioning phase are presented in Figure 1. Startle magnitude showed different patterns of change from Session 1 to Session 2 in the two groups (Group × Session), $F(1, 22) = 22.2$, $p < .0009$. Startle was significantly decreased from Session 1 to Session 2 in the non-PTSD group, $F(1, 22) = 6.4$, $p < .01$, whereas it was significantly increased in the PTSD group, $F(1, 22) = 4.2$, $p < .05$. There was no other significant group difference. In particular, the Group × Phase × Session interaction was not significant, $F(2, 44) = 0.72$.

Animal studies have indicated that aversive shocks can sensitize startle for relatively short (Davis, 1989; Leaton & Cranney, 1990) or long (Gewirtz, McNish, & Davis, 1998; Servatius, Ottenweller, & Natelson, 1995) periods. The design of the present experiment did not permit a specific analysis of shock sensitization. Nevertheless, we examined whether there was a differential modulation of baseline startle (i.e., ITI startle) between groups following shock administration in Session 1 by comparing the pre- and postconditioning ITI data by using a Group (non-PTSD, PTSD) × Phase (preconditioning, postconditioning) ANOVA. The results indicated that startle was not increased by the shocks in Session 1. In fact, startle habituated similarly in the two groups, $F(1, 22) = 14.6$, $p < .001$, for phase, and $F(1, 22) = 0.07$ for Group × Phase. In the non-PTSD group, startle during the ITI (averaged over blocks) was reduced from 191 μV in the preconditioning phase to 148 μV

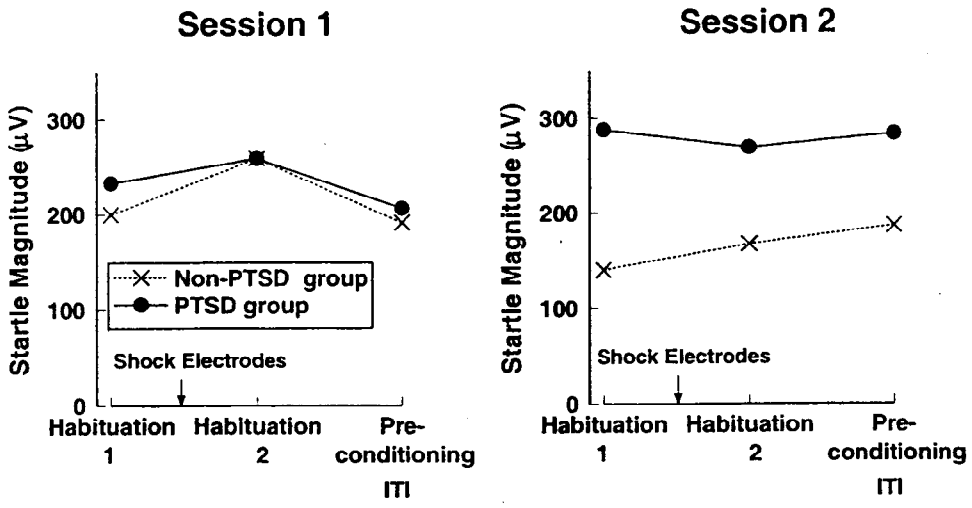

Figure 1. Baseline startle magnitude in Session 1 and Session 2. Startle magnitude in veterans with posttraumatic stress disorder (PTSD) and veterans without PTSD (Non-PTSD) during Habituation 1, Habituation 2, and the intertrial interval (ITI) of the preconditioning phase of Session 1 and Session 2 are shown. The arrow indicates when the shock electrodes were attached to the participants.

in the postconditioning phase. A similar pattern of reduction from 206 to 155 μV was seen in the PTSD group. Equivalent results were obtained when only startles during the ITI of the last block of conditioning and during the ITI of the first block of postconditioning were analyzed.

Explicit Cue Conditioning During Session 1

Figure 2 shows the magnitudes of startle during the preconditioning, conditioning, and postconditioning phases of Session 1 for the non-PTSD and PTSD groups.

Preconditioning phase. There was an unexpected increase in startle during the CSs in the preconditioning phase. A Group (2) × Trial Type (ITI vs. [CS+, CS−]) × Block (2) ANOVA revealed a significant trial type main effect, $F(1, 22) = 5.6$, $p < .02$. Although this effect appeared to be greater in Block 1 than in Block 2, the Trial Type × Block interaction was not significant, $F(1, 22) = 1.1$. Importantly, this effect did not differ significantly between the two groups (Group × Trial Type), $F(1, 22) = 0.4$. An additional analysis comparing startle during the CS+ and the CS− was performed: Group (2) × Trial Type (CS+ or CS−) × Block (2). Neither the trial type, $F(1, 22) = 0.0009$, nor the Group × Trial Type interaction, $F(1, 22) = .24$, was significant, suggesting that the two CSs did not affect startle differentially prior to conditioning.

Conditioning phase. Startle magnitude was greater during the CS+ than during the CS− (trial type [CS+ or CS−]), $F(1, 22) = 4.4$, $p < .05$. This effect tended to be greater in Block 2 (Trial Type × Block), $F(1, 22) = 3.6$, $p = .07$. Although the pattern of means suggests greater conditioning in the non-PTSD group than in the PTSD group (Figure 2), this difference was not statistically reliable (Trial Type × Group), $F(1, 22) = 3.0$, $p = 0.10$. This lack of significant interaction might have been attributable to a lack of statistical power and/or to the fact that the distribution of the startle probes during acquisition was not optimal for detecting differential conditioning. For these reasons, within-group CS+ versus CS− comparisons were performed to examine whether conditioning occurred in the non-PTSD group. Startle was significantly greater during the CS+ than during the CS− in the non-PTSD group, $F(1, 22) = 7.0$, $p = 0.01$, but not in the PTSD group, $F(1, 22) = 1.2$. A comparison between startle responses during the ITI and the CS− revealed a trend for a Group × Trial Type interaction, $F(1, 22) = 4.0$, $p < .057$, that was attributable to the fact that startle tended to be greater during the CS− than during the ITI in the PTSD group, $F(1, 22) = 2.9$, $p = .10$, but not in the non-PTSD group, $F(1, 22) = 0.01$.

Postconditioning phase. As shown in Figure 2, startle responses during the CS+ and the CS− differed between the two groups during postconditioning (Trial Type × Group), $F(1, 22) = 6.0$, $p < .02$. There was successful differential conditioning (i.e., greater startle during the CS+ than during the CS−) in the non-PTSD group (trial type [CS+, CS−]), $F(1, 22) = 11.8$, $p < .002$, but not in the PTSD group, $F(1, 22) = 1.5$. The same pattern of statistically significant effects was obtained when the analysis was restricted to postconditioning Block 1, suggesting that the failure to obtain reliable conditioning in the PTSD group was not attributable to rapid extinction.

The lack of differential conditioning in the PTSD group was attributable to the fact that the startle response in this group was potentiated by the CS− relative to the ITI. A comparison of startle during the ITI and the CS− revealed a significant Group × Trial Type interaction, $F(1, 22) = 7.4$, $p < .01$, reflecting a relative increase in startle magnitude during the CS− compared to the ITI in the PTSD group, $F(1, 22) = 11.3$, $p < .003$, but not in the non-PTSD group, $F(1, 22) = 0.8$.

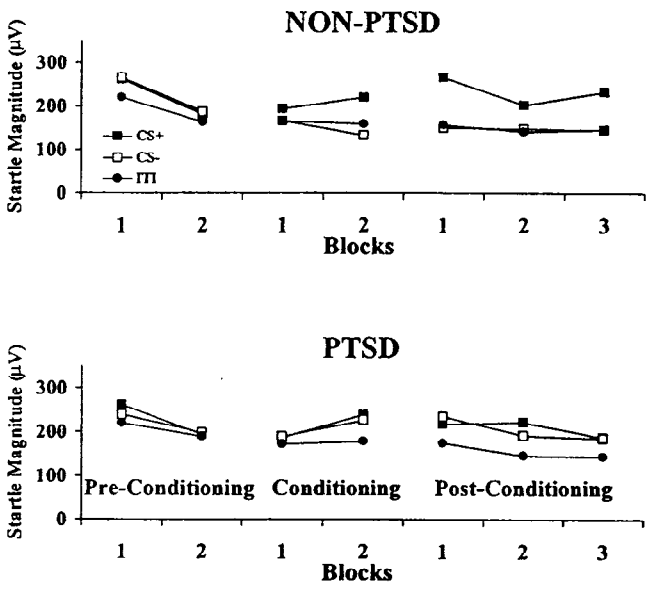

Figure 2. Results of conditioning in the non-posttraumatic stress disorder (NON-PTSD) and PTSD groups in Session 1. CS+ = conditioned stimulus with unconditioned stimulus (US); CS− = conditioned stimulus without US; ITI = intertrial interval.

Retention of Conditioning and Reconditioning During Session 2

Preconditioning phase. Figure 3 shows the results obtained during Session 2 for the non-PTSD and PTSD groups. Although, as noted previously, the experimental context affected the two groups differently at the beginning of Session 2, both groups showed a potentiation of startle during the CSs. The analysis comparing the CS+ to the CS− indicated a nearly significant Group × Trial Type (CS+, CS−) interaction, $F(1, 22) = 4.0$, $p < .057$, for raw scores, and $F(1, 22) = 6.4$, $p < .01$, for z scores. However, this effect did not reflect a genuine group difference in the retention of differential conditioning. Follow-up tests showed that startle was not significantly greater during the CS+ than during the CS− in the non-PTSD group, $F(1, 22) = 1.3$ for raw scores, whereas the opposite was true in the PTSD group, $F(1, 22) = 0.4$.

Conditioning phase. In contrast to the findings from Session 1, the PTSD group showed differential startle potentiation to the CS+ and the CS− during conditioning in Session 2. Thus, the magnitude of startle was significantly greater during the CS+ than during the CS− in both groups (Figure 3), $F(1, 22) = 6.3$, $p < .01$, for trial type (CS+ or CS−), and $F(1, 22) = 0.01$, *ns*, for Group × Trial Type.

Postconditioning phase. Differential startle potentiation to the CS+ and the CS− lasted throughout the postconditioning phase in

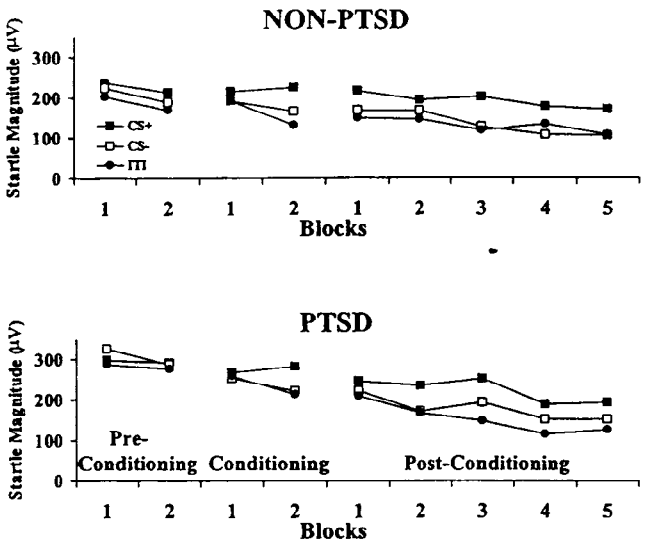

Figure 3. Results of conditioning in the non-posttraumatic stress disorder (NON-PTSD) and PTSD groups in Session 2. CS+ = conditioned stimulus with unconditioned stimulus (US); CS− = conditioned stimulus without US; ITI = intertrial interval.

both groups. Statistical analyses indicated a significant trial type (CS+ or CS−) main effect, $F(1, 22) = 17.1$, $p < .0009$, and a nonsignificant Trial Type × Group interaction, $F(1, 22) = 1.0$. There was no evidence of extinction of differential conditioning in either group: ($F(1, 22) = 0.4$ for Trial Type × Block, and $F(1, 22) = 0.3$ for Group × Trial Type × Block.[3] There was a small but significant increase in startle magnitude during the CS− compared to the ITI in both groups (trial type), $F(1, 22) = 6.9$, $p < .01$. Although this effect appeared to occur mostly in the PTSD group, the Group × Trial Type interaction was not significant, $F(1, 22) = 0.1$.

Questionnaires

Anxiety ratings. State anxiety and trait anxiety are shown in Table 1. State anxiety was investigated with a Group × Session ANOVA. State anxiety was significantly higher in the PTSD group than in the non-PTSD group, $F(1, 22) = 31.4$, $p < .0009$, but did not change significantly from Session 1 to Session 2. The Group × Session interaction was not significant, $F(1, 22) = .01$. Trait anxiety was significantly higher in the PTSD group than in the non-PTSD group, $t(22) = 3.7$, $p < .001$.

Verbal awareness of the CS–US relationship. In Session 1, 11 of the 12 veterans without PTSD correctly indicated the CS–US relationship. The remaining veteran without PTSD stated that he did not know the relationship. Eleven of the 12 veterans with PTSD also identified the correct CS–US relationship. The remaining veteran with PTSD indicated that the shocks were not delivered in a systematic manner. This individual was also the only one who could not correctly identify the CS–US relationship in Session 2. He again indicated that the shocks were not delivered in a systematic manner.

Discussion

The two main findings of this study were that veterans with PTSD did not show differential conditioned startle responses during the initial acquisition session and exhibited increased startle from Session 1 to Session 2. These results are consistent with several aspects of our other findings (Grillon et al., 1998) that have shown that stress potentiates startle in veterans with PTSD. Possible mechanisms mediating these effects include stimulus generalization, contextual fear, and sensitization and will be discussed below.

The finding of greater startle during the CS+ than during the CS− in the conditioning and postconditioning phases of Session 1 for the veterans without PTSD is consistent with recent studies indicating that startle is an effective measure of aversive conditioning (Hamm, Greenwald, Bradley, & Lang, 1993; Hamm & Vaitl, 1996). A major finding of this study is that this differential startle response was not observed in the veterans with PTSD who showed potentiated startle to both the CS+ and the CS−. This lack of differential conditioning in the PTSD group did not seem to be attributable to a failure to pay attention to the CSs or to a failure to learn the CS–US contingency. All but one patient correctly reported the correct association between the CS+ and the shock, indicating a normal declarative knowledge of the learning procedure. These results raise the possibility of a dissociation between cognitive awareness of the relationship between the CS and the US and emotional responses in veterans with PTSD.

The lack of a differential startle response during the CS+ and the CS− in Session 1 was attributable to the presence of an increase in startle during the CS− (relative to the ITI). This inability to reduce fear to what should have been considered a safety signal (because of the knowledge that the CS− was not associated with the shock) could have been attributable either to deficits in mechanisms associated with fear inhibition or to learning impairments. From a practical standpoint, these results suggest that veterans with PTSD tend to react with fear and anxiety to innocuous events presented in stressful contexts.

The fact that additional training (in Session 2) resulted in successful differential conditioning indicates that the veterans with PTSD could meaningfully distinguish between threat and safety cues and activate fear-inhibitory mechanisms. These results suggest that PTSD might be associated more with deficits in learning safety cues than in deficits in the activation of mechanisms of fear inhibition per se. In fact, this hypothesis is supported by our other findings obtained with verbal threat procedures (Grillon et al., in press; Morgan et al., 1995). When veterans with PTSD did not have to learn experientially the difference between safety and threat signals (because of explicit instruction), differential startle responses to safety and threat signals were observed.

Not surprisingly, given their lack of differential conditioning during Session 1, the veterans with PTSD did not show differential responses to the CS+ and the CS− in the preconditioning phase of Session 2. However, the observation that the veterans without PTSD no longer showed a significant increase in startle during the

[3] The successful conditioning in the PTSD group was not due to a subset of participants. Eleven of the 12 veterans with PTSD had a greater magnitude of startle during the CS+ than during the CS−. For comparison, only 5 of 12 veterans with PTSD showed such an effect in Session 1.

CS+ compared to the CS− during this period was unexpected, as previous studies have shown that skin conductance measures of conditioning are fairly well retained (Schell, Dawson, & Marinkovic, 1991). One possibility is that the absence of a significant difference was attributable to the relative lack of power of the statistical analysis. Another possibility is that the skin conductance and the startle reflex index different processes during conditioning (e.g., awareness of the CS–US relationship and affective responses, respectively; Hamm & Vaitl, 1996). These processes might be differentially affected by the passage of time. In fact, the current data are consistent with the findings of animals studies showing that conditioned fear tends to be generalized over time (Hendersen, 1978; Mineka & Tomarken, 1989).

The second major finding of the study was the increase in startle from Session 1 to Session 2 in the veterans with PTSD. There are several possible explanations for such a result. Animal studies have demonstrated aversive context conditioning, that is, an increase in fear in an environment in which the animals have experienced aversive events (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). For example, startle can be increased when animals are reintroduced to a cage in which they received shocks previously (Gewirtz, Falls, & Davis, 1997; McNish, Gewirtz, & Davis, 1997). A similar effect has been reported for humans tested in an experimental room in which they received shocks a few days earlier (Grillon & Davis, 1997). Hence, the increase in baseline startle in Session 2 in the veterans with PTSD may reflect contextual fear conditioning. Enhanced contextual fear conditioning in the veterans with PTSD may also reflect the tendency of veterans with PTSD to generalize fear across stimuli. As the differential conditioning data attest, such a tendency was already present in Session 1. The passage of time might have exaggerated this process (Hendersen, 1978; Mineka & Tomarken, 1989). Clinically, fear in response to specific war-related cues seems to be generalized to non-war situations over time. As stated by a veteran with PTSD, "At first, when I got back I was just nervous to loud sounds, then I started to develop all kinds of fears or phobias to just about everything."

Until recently, neurophysiological studies with "freezing" as a measure of fear have supported the ideas that the amygdala is involved in both explicit cue conditioning and context conditioning and that the hippocampus is involved only in context conditioning (Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Wilkinson, Humby, Robbins, & Everitt, 1995). At present, however, there is conflicting evidence concerning the role of the hippocampus in context conditioning. For example, lesions of the hippocampus disrupted freezing but did not affect potentiated startle in a context in which footshock had been given previously (McNish, Gewirtz, & Davis, 1997). Thus, lesions of the hippocampus might not affect context conditioning but might produce an unconditioned effect that interferes with freezing. Similarly, questions have been raised about the involvement of another structure, the BNST (Davis, Gewirtz, McNish, & Kim, 1995), in context conditioning. Recent studies have indicated that context conditioning is blocked by chemical inactivation of the BNST with the glutamate antagonist NBQX (M. Davis, personal communication, May 1998), but is not affected by lesions of the BNST (McNish, Gewirtz, & Davis, 1996). Presently, the amygdala is the only structure that is widely accepted as having a critical role in contextual fear conditioning (and explicit cue conditioning).

An alternative explanation for the increase in baseline startle in Session 2 in the veterans with PTSD is that it reflects an unconditioned, rather than a conditioned, process. Startle could have been sensitized by the stress of Session 1 and, more particularly, by the administration of shocks. Two types of shock sensitization of startle have been identified on the basis of their temporal appearance and their underlying brain structures (Davis, 1989; Gewirtz et al., 1998; Servatius et al., 1995). In rats, exposure to footshock produces a relatively rapid and transient sensitization of startle (Davis, 1989). Recently, Gewirtz et al. (1998) reported a more gradual elevation of baseline startle that occurs over successive days of training (CS–US). Lesions of the BNST block the gradual sensitization of startle but do not disrupt the rapid sensitization of startle, which is blocked by lesions of the amygdala (Sananes & Davis, 1992). In fact, there is now evidence that the rapid shock sensitization of startle in a single day of training is a form of contextual fear conditioning (Kiernan, Westbrook, & Cranney, 1995). The gradual sensitization of startle over the course of several days of training appears to be an unconditioned response to the cumulative effect of chronic stress (Gewirtz et al., 1998), possibly mediated by the BNST following the release of the stress hormone corticotropin-releasing hormone (CRH; Lee & Davis, 1996). Thus, the increase in baseline startle in Session 2 in the veterans with PTSD may reflect an unconditioned stress response caused by exposure to shocks in Session 1. For example, it is possible that the stress of Session 1 led to persistent and lasting worries about upcoming Session 2, resulting in a release of CRH and to an increase in anxiety levels. The finding of abnormal levels of cerebrospinal fluid CRH concentrations in veterans with PTSD provides some support for this hypothesis (Darnell et al., 1994).

The data from this study may provide support for the context conditioning hypothesis but not the unconditioned stress response hypothesis. Baseline startle tended to be greater in the veterans with PTSD than in the veterans without PTSD, $F(1, 22) = 2.8, p < .10$, at the beginning of Session 2 (Habituation 1, Habituation 2, and preconditioning phase), but this difference was no longer present during the conditioning and postconditioning phases, suggesting that baseline startle normalized as the experiment went on. This normalization of baseline startle does not seem to be compatible with an interpretation involving a lasting effect of unconditioned stress. Rather, it is consistent with the alternative view of context conditioning. Indeed, as the veterans with PTSD learned to fear the explicit CS+, one would have expected their contextual fear to decrease.

The findings of this study may be relevant to the distinction made by some (American Psychiatric Association, 1994; LeDoux, 1992; Maeda, 1993) between fear and anxiety. Fear is elicited by a clearly identifiable source, whereas free-floating anxiety is not. It is possible that explicit threat cues produce fear, whereas contextual stressful stimuli or long-term sensitization elicits an affective response more akin to anxiety. The former affective response might be more relevant to anxiety disorders with an identifiable fear (specific phobia), whereas the latter might be more relevant to disorders such as panic disorder and general anxiety disorders (Cuthbert, Bradley, & Lang, 1996). PTSD would seem to involve elements of both, as both explicit stimuli reminiscent of traumatic experiences and stressful contexts produce substantial distress.

Finally, several cautionary comments are in order. First, the veterans with PTSD did not show contextual fear, as assessed by

verbal reports (state anxiety scores). Among the possible explanations for such a finding is the fact that state anxiety and startle were assessed at different times. State anxiety was assessed early in the experiment, in the absence of some of the contextual cues (e.g., headphone, startle sound) that might have contributed to the contextual fear conditioning results. It is also possible that the Spielberger (1983) state form of the State–Trait Anxiety Inventory is less sensitive for detecting context conditioning than is the startle reflex. Finally, as mentioned above, startle may be modulated by processes that are beyond conscious awareness (Hamm & Vaitl, 1996).

A second note of caution is that, given the nature of our experiments, participants who agreed to be involved in the study may not be truly representative of all veterans with PTSD. In this study, the only participant who did not return for Session 2 was a veteran with PTSD and with a greatly exaggerated startle and elevated trait anxiety and Mississippi scores. This fact suggests that patients with more severe symptoms did not participate in our experiments. Hence, if anything, this study may have underestimated, not overestimated, differences between the PTSD and non-PTSD groups.

A third note of caution is that it is unknown to what extent our results are specific for PTSD, given that increased baseline startle has been reported for patients with panic disorder and participating in a threat-of-shock experiment (Grillon, Ameli, Goddard, Woods, & Davis, 1994). This fact suggests that contextual fear may also characterize other anxiety disorders.

To summarize, our results indicate that veterans with PTSD are slow to acquire differential conditioned responses and show enhanced contextual fear conditioning or sensitization to stress. The interpretation of these results is still tentative and, ultimately, the elucidation of their meaning depends on future studies with both animals and humans. Animal studies might attempt to clarify the similarities and differences in the brain mechanisms mediating explicit cue context, context conditioning, and short- and long-term sensitization, as these processes are relevant to PTSD as well as to other anxiety disorders (Grillon et al., 1994). Human investigations should further assess the relationships between cognitive awareness of the CS–US relationship and affective responses. The use of multiple physiological measures will be helpful in this regard. The skin conductance response might be particularly indicated because it is closely linked to cognitive processes during conditioning (Dawson & Furedy, 1976). Improving the understanding of context conditioning and unconditioned sensitization processes is also an area for further research. Despite the fact that this study leaves numerous issues unresolved, it raises important questions and encourages the use of the startle methodology in future studies.

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